PROTEIN REFINEMENT: A NEW CHALLENGE FOR CASP IN ITS 10TH ANNIVERSARY

The CASP community-wide assessment of protein structure prediction methods (CASP6, 2004, http://predictioncenter.llnl.gov/casp6/) anniversary coincides with a general realization of the need to speed progress, and achieve sustained success in protein structure prediction [see the NIGMS-NIH new initiative for improving protein structure prediction methods (http://www.nigms.nih.gov/)], toward which CASP has substantially contributed. Unfortunately, so far progress has not been as continuous as in other fields of technology, perhaps indicating that substantial new scientific contributions are still required.

Interestingly, the recent CASP edition has shown a small but substantial progress in the quality of the corresponding sequence to structure alignments, particularly for modeling based on the structure of similar proteins (commonly known as homology modeling), which is the area most directly applicable to biology. This improvement is not only related to the new generation of sequence-based methods (e.g. profile–profile alignments), but also to the pure growth of the sequence databases, as shown for previous CASP editions (Cozzetto and Tramontano, 2005).

What is particularly interesting is that this progress does not seem to be directly followed by an obvious improvement in the quality of the models derived from those alignments, indicating that substantial work would have to be dedicated to the development of methods for the refinement of structural models. If this tendency can be confirmed, refinement after identification of sequence–structure alignment would soon become a bottleneck for making protein structure prediction methods useful for biology. From what we have seen in CASP6, solutions may be in reach, e.g. in at least one case David Baker’s group (University of Washington) managed to substantially improve the structure of a model, that they had built for a very difficult protein, with no homologs in the database, using a standard full-atom force field.

The CASP community has shown a genuine interest in directly addressing this new challenge, but the specific computational demands required by the refinement programs certainly pose an interesting challenge to the organization of CASP as it enters its second decade.

REFERENCES

CASP6 was organized by A. Tramontano, University of Rome. The CASP organizing committee is formed by: J. Moult (President) CARB, University of Maryland; K. Fidelis, Lawrence Livermore National Laboratory; T. Hubbard, Wellcome Trust Sanger Institute, Hinxton; B. Rost, Columbia University; A. Tramontano, University of Rome. CASP6 assessors were A. Valencia, CNB-CSIC, Madrid; R. Dunbrack, Fox Chase Cancer Center, Philadelphia; B.K. Lee, NCI/NIH, Bethesda. Cozzetto, D. and Tramontano, A. (2005) Relationship between multiple sequence alignments and quality of protein comparative models. *Proteins, 58*, 151–157.

Alfonso Valencia
Bioinformatics, Co-Executive Editor
Protein Design Group
Centro Nacional de Biotecnologia-CSIC Darwin 3
Cantoblanco
Madrid 28049, Spain
Email: valencia@cnb.uam.es
Received on December 13, 2004; accepted on December 20, 2004
Advance Access publication January 12, 2005